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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/884,873	06/30/1997	PHILLIP DAN COOK	ISIS-2202	6678

7590 12/24/2002

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BAKER, MAURIE GARCIA

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/24/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>08/884,873</b>	Applicant(s) <b>Cook</b>
	Examiner <b>Maurie G. Baker, Ph.D.</b>	Art Unit <b>1639</b>

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1)  Responsive to communication(s) filed on Oct 3, 2002

2a)  This action is **FINAL**.      2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 835 C.D. 11; 453 O.G. 213.

#### Disposition of Claims

4)  Claim(s) 2-5, 7-12, and 33 is/are pending in the application.

4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 2-5, 7-12, and 33 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____	6) <input type="checkbox"/> Other: _____

## DETAILED ACTION

**Please note:** The number of Art Unit 1627 has been changed to 1639. Please direct all correspondence for this case to **Art Unit 1639**.

1. The Response filed on October 3, 2002 (Paper No. 29) is acknowledged. No claims were amended, cancelled or added. Therefore, claims 2-5, 7-12 and 33 are pending and under examination.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 33 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what is the specific structure of the compounds of formula I because the L moiety is *incompletely defined*. For example, if L is a moiety such as “keto”, “carboxyl” or “amidine”, what is the actual structure of such a group? That is, denoting the group as “keto” (for example) does not fully define what ketone is being referred to. The same is true for many of the moieties listed for the instant L group. This adds considerable confusion to the claim.

***Response to Arguments***

4. Applicant's arguments filed October 3, 2002 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

5. Applicant argues that a person of ordinary skill in the art would "know what structure corresponds to each group" and that one of ordinary skill would "readily understand" the claim as written (Response, page 2). The examiner agrees that one of ordinary skill would indeed know whether a certain compound contains a "keto" group or not, *when presented with a specific structure*. However, the question is what is the actual structure of such a group in the instant claims. That is, denoting the L group as "keto" (for example) in the claims does not fully define what ketone is being referred to or how it is attached to the rest of the compound. Applicant's claims contain the L moieties as a variable group of part of a larger structure.

6. Please note that if the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

7. Thus, for the reasons set forth above and the reasons of record, the rejection under 35 U.S.C. 112, second paragraph is maintained.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 2-5, 7-12 and 33 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gordeev et al (WO 96/33972), Grandoni (US 5,998,420) and Hamprecht et al (US 5,591,694) in view of Gordon et al (of record, J. Med. Chem. 1994, Vol. 37, No. 10, pp. 1385-1401).

Gordeev et al teach methods for synthesizing libraries of pyrimidine compounds (see Abstract). The library compounds of Gordeev et al have the claimed heterocyclic scaffold and substitution pattern (see page 34-35 and more specifically page 81) and are substantially homogeneous (page 35, bottom). The library compounds are made in a pooled format (see page 84, lines 18-28), for example, a pool of 21 pyrimidines is made and tested. This reads directly on the limitation of a mixture of at least 6 compounds and the further limitations of claims 2 and 3. All compounds are present in at least some of the pools and the compounds are synthesized at a purity (see page 81) where the mixture would be close to equimolarity. The pyrimidine compounds of Gordeev et al have at least three functionalizable atoms, at least one of which is nitrogen (see pages 81-85). In the compounds of Gordeev et al the tethers can be considered to be bonds for

two of the side groups and the amine moiety could be considered a tether moiety ( $\text{NHR}^1$ ). This meets the limitations of claims 5 and 7-10. The building blocks of the library comprise various leaving groups (see page 83), reading on the limitations of claims 11 and 12.

Gordeev et al lacks the specific teaching of the instantly claimed compounds of the library (specific T and L combinations).

However, Grandoni et al teach sulfonylurea herbicides that read on the claimed compounds (see Figures 3 & 5, for example). The pyrimidine compounds have least three functionalizable atoms, at least one of which is nitrogen, oxygen and/or sulfur and have groups that can be considered tethers (see structures S, T, U and V in Figure 5 and compound at the bottom of Figure 6). The building blocks of the library comprise various leaving groups (see column 9, top). In the context of creating better inhibitors of acetolactate synthase (beginning in column 8 and going through the top of column 10), Grandoni et al teach the concept of "combinatorial optimization of inhibitory sulfonylureas" (column 9).

Hamprecht et al also teach sulfonylurea herbicides (see Abstract). These compounds also read on those in the claimed mixture and have similar substitution to those of Grandoni. Hamprecht et al teach that compounds with improved properties are needed and that to do so, varying the substituents on the pyrimidine moiety is a preferred method of doing so (see column 2, lines 12-23).

Grandoni and Hamprecht et al lack the teaching of creating a mixture of at least 6 compounds.

However, Gordeev et al teach these limitations, see above. Also, Gordon et al teaches that “[w]hen small molecule leads for a target have been previously defined...the notion of searching for more potent derivatives among libraries combinatorially enriched in specific pharmacophore analogs is an obvious tactic to pursue” (p.1386 Column 1, 1<sup>st</sup> full paragraph). Also, Gordon et al teaches the general principles of combinatorial chemistry and the rationale for creating libraries, see page 1385 and 1397-1401 generally. Specifically, the notion of intentional biasing as a form of drug design is taught (see page 1401, 1<sup>st</sup> column). Gordon et al teaches a “spectrum of molecular diversity” (see page 1397, Figure 19) that describes why a library of a certain size would be useful for a variety of different applications.

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create a mixture (i.e. library) of six or more compounds of the claimed type based on the teachings Grandoni and Hamprechet et al as to the synthesis and uses of such compounds and the teachings of Gordeev et al and Gordon et al regarding libraries. A person of ordinary skill in the art would have been motivated to create libraries to have large numbers of molecules available for testing for improved properties (see Gordon, page 1398, 1<sup>st</sup> paragraph).

#### *Response to Arguments*

10. Applicant’s arguments filed October 3, 2002 have been fully considered but are not found persuasive. The examiner’s rationale is set forth below.

11. Applicant argues that the “combination of the references does not produce the claimed invention” (Response, page 3, top). In response to this argument, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

12. As stated in the rejection, there are several references that teach the core pyrimidine scaffold compound of structure I, along with the claimed substitution pattern. Although no single reference teaches a set of at least six compounds that have both T and L moieties as claimed, the examiner’s position is that it would have been obvious to create such a set (i.e. library) to have large numbers of molecules available for testing for improved properties (see Gordon, page 1398, 1<sup>st</sup> paragraph). Moreover, two of the cited references that teach pyrimidine compounds (i.e. Gordeev et al and Grandoni et al) *specifically* teach making libraries of compounds.

13. Applicants also argue that none of the cited references specifically disclose compounds that read on the claimed pyrimidine compounds (Response, pages 3-4). As stated in the rejection, the pyrimidine compounds of Gordeev et al have at least three functionalizable atoms, at least one of which is nitrogen. In the compounds of Gordeev et al the tethers (T) can be considered to be bonds for two of the substituents and NH for

the other. The moieties Thus, the difference between the compounds of Gordeev et al and the claims is the presence of a T moiety for two of the three substituents. Note that for the substituents that do not contain a T as claimed, the remaining portions of the compounds of Gordeev et al *would* read on the instant L moieties. The other two references that teach pyrimidine compounds also teach the claimed substitution pattern, and *do* teach moieties that would read on the claimed T moiety at each of the three positions. For example, the compounds denoted **IIIId** in column 6 of Hamprecht et al have moieties that read on the instant T = O, O and NH, respectively. Grandoni et al also teach compounds that have moieties that read on the instant T = O, O and NH, respectively (see, for example, the first compound listed in Figure 3 of the reference).

14. Thus, the examiner's position is that the combined teachings of the references would have suggested the claimed pyrimidine compounds and substitution pattern, along with the use of moieties reading on the claimed T moiety to link substitutents thereto, to those of ordinary skill in the art. This is especially true when coupled with the teachings of Gordon et al with respect to libraries ("[w]hen small molecule leads for a target have been previously defined...the notion of searching for more potent derivatives among libraries combinatorially enriched in specific pharmacophore analogs is an obvious tactic to pursue").

15. Furthermore, it is also the examiner's position that the references *do* specifically disclose compounds that read on the claimed pyrimidine compounds. For example, if

one considers the definition of R<sup>1</sup> in Hamprecht et al (i.e. column 2) the compounds denoted **IIIId** in the reference *would* read on those of claim 33. Also, Grandoni et al teaches “Combinatorial Synthesis of Sulfonylureas” (see column 9, top) where the reactants denoted R<sub>3</sub>-NH-R<sub>2</sub> would read on the compounds of claim 33 when R<sub>3</sub> of the reference is hydrogen and R<sub>2</sub> is the moiety denoted S from Figure 5. Thus, the teachings above, combined with the teaching of libraries of pyrimidine compounds by Gordeev et al and the general teachings of Gordon et al, also would have suggested the claimed invention to those of ordinary skill in the art.

16. Thus, for the reasons set forth above and the reasons of record, the rejection under 35 U.S.C. 103(a) is maintained.

***Status of Claims/Conclusion***

17. No claims are allowed.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the

date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.  
December 20, 2002



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